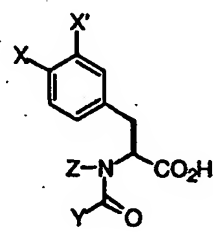


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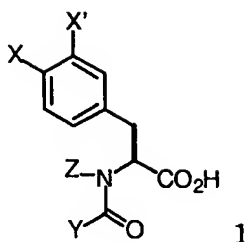
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07C 233/87, 235/52, 237/36, 317/50, 323/39, C07D 215/50, 233/32, 295/088, 487/04, A61K 31/165, 31/33 // C07D 487:04, 239:00, 231:00</p>	A1	<p>(11) International Publication Number: <b>WO 99/10312</b></p> <p>(43) International Publication Date: 4 March 1999 (04.03.99)</p>
<p>(21) International Application Number: PCT/EP98/05135</p> <p>(22) International Filing Date: 13 August 1998 (13.08.98)</p> <p>(30) Priority Data: 60/056,718 22 August 1997 (22.08.97) US</p> <p>(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).</p> <p>(72) Inventors: CHEN, Li; 6 Drummond Road, Westfield, NJ 07090 (US). GUTHRIE, Robert, William; 102 Alberta Drive, Saddle Brook, NJ 07663 (US). HUANG, Tai-Nang; 67 Sherburne Road South, Lexington, MA 02173 (US). HULL, Kenneth, G.; 143 River Road, Clifton, NJ 07014 (US). SIDDURI, Achyutharao; 22 Washington Court, Livingston, NJ 07039 (US). TILLEY, Jefferson, Wright; 19 Evergreen Drive, North Caldwell, NJ 07006 (US).</p> <p>(74) Agent: LOESCHNER, Thomas; Grenzacherstrasse 124, CH-4070 Basle (CH).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. With amended claims.</p>
<p>(54) Title: N-ALKANOYLPHENYLALANINE DERIVATIVES</p> <div style="text-align: center;">  <p>(1)</p> </div> <p>(57) Abstract</p> <p>Compounds of formula (1) as well as their salts and esters are disclosed wherein X, X', Z and Y are as described in the specification and which have activity as inhibitors of binding between VCAM-1 and cells expressing VLA-4. Such compounds are useful for treating diseases whose symptoms and/or damage are related to the binding of VCAM-1 to cells expressing VLA-4.</p>		

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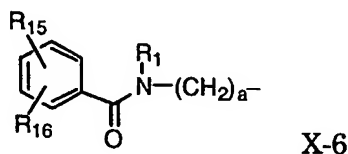
Claims

1. A compound of the formula:



5 wherein:

one of X and X' is hydrogen, halogen, or lower alkyl, the other is a group of the formula:



wherein:

10 R<sub>1</sub> is hydrogen or lower alkyl,

R<sub>15</sub> is halogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, OH, lower alkoxy, lower alkoxy carbonyl, carboxy, lower alkyl aminosulfonyl, perfluorolower alkyl, lower alkylthio, hydroxy lower alkyl, alkoxy lower alkyl, halo lower alkyl, alkylthio lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, lower alkyl, lower alkylsulfinyl, lower alkanoyl, aroyl, aryloxy or a group of the formula R<sub>17</sub>-C≡C-,

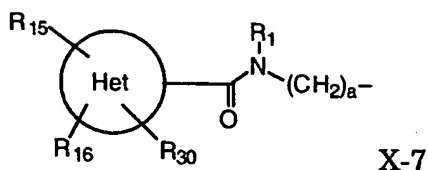
R<sub>16</sub> is hydrogen, halogen, nitro, cyano, lower alkyl, OH, perfluorolower alkyl, or lower alkylthio,

R<sub>17</sub> is hydrogen, aryl, heteroaryl, or lower alkyl which is unsubstituted or substituted by OH, aryl, or heteroaryl, and

a is 0 or 1;

or one of X and X' is a group of the formula:

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wherein Het is a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S;

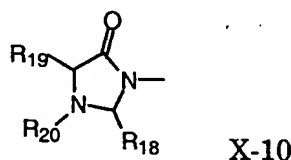
or

- 5 Het is a 9- or 10-membered bicyclic heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms selected from O, S, and N,

a, R<sub>1</sub>, R<sub>15</sub> and R<sub>16</sub> are as above, and

R<sub>30</sub> is hydrogen or lower alkyl, or is absent;

or one of X and X' is a group of the formula:



10

wherein:

R<sub>18</sub> is lower alkyl, aryl, heteroaryl, arylalkyl, heteroaryl alkyl,

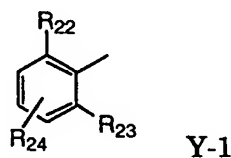
- R<sub>19</sub> is lower alkyl, which is unsubstituted or substituted by one or more of halogen, hydroxy, lower alkoxy, aryl, heteroaryl, alkylthio, or R<sub>19</sub> is aryl or  
15 heteroaryl, and

R<sub>20</sub> is lower alkyl or lower alkanoyl, or

R<sub>19</sub> and R<sub>20</sub> taken together are tetramethylene;

and

Y is a group of the formula:

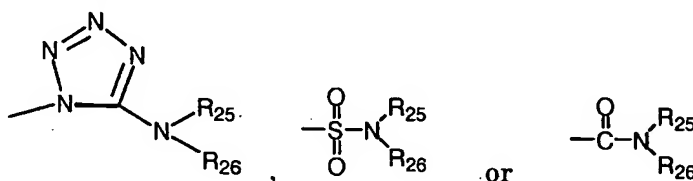


20

wherein:

R<sub>22</sub> and R<sub>23</sub> are independently hydrogen, lower alkyl, lower alkoxy, lower alkoxyalkyl, lower alkylamino, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or  
 5 perfluoroalkyl and at least one of R<sub>22</sub> and R<sub>23</sub> is other than hydrogen, and

R<sub>24</sub> is hydrogen, hydroxy, lower alkyl, lower alkoxy, amino, aryl, nitro, cyano, lower alkyl sulfonyl, halogen, or is a group of the formula:



wherein R<sub>25</sub> is hydrogen, lower alkyl, aryl, aryl lower alkyl, alkoxy lower  
 10 alkyl and R<sub>26</sub> is hydrogen or lower alkyl, or

R<sub>22</sub> and R<sub>24</sub> taken together are a fused benzene ring; or

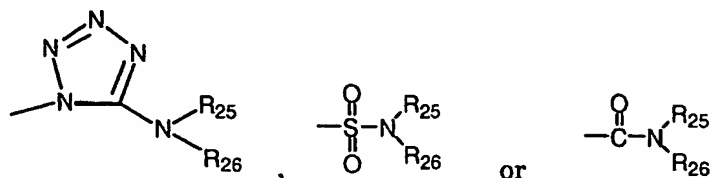
Y is a group Y-2 which is a five or six membered monocyclic heteroaromatic group containing 1, 2 or 3 heteroatoms selected from N, O, and S, or a 9- or 10-membered bicyclic heteroaromatic group containing 1, 2, 3 or 4  
 15 heteroatoms selected from O, S, and N, wherein said heteroaromatic group is bonded via a carbon atom to the amide carbonyl and one or two carbon atoms of said heteroaromatic group are substituted by lower alkyl, halogen, cyano, perfluoroalkyl, or aryl and at least one of said substituted carbon atoms is adjacent to the carbon atom bonded to the amide carbonyl;  
 20 and the pharmaceutically acceptable salts and esters thereof.

2. A compound according to claim 1, wherein Z is hydrogen.

3. A compound according to claim 1 or 2, wherein X' is hydrogen.

4. A compound according to any one of claims 1-3, wherein:  
 R<sub>22</sub> and R<sub>23</sub> are independently hydrogen, lower alkyl, nitro, lower alkylthio,  
 25 lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluoroalkyl wherein at least one of R<sub>22</sub> and R<sub>23</sub> is not hydrogen, and

R<sub>24</sub> is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkylsulfonyl, amino, nitro, halogen or a group of the formula:

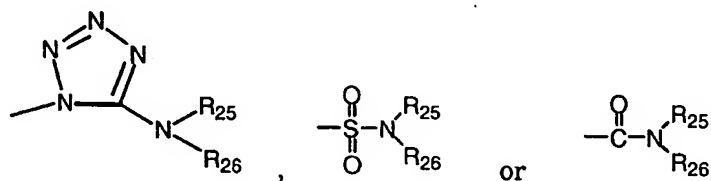


wherein R<sub>25</sub> is aryl lower alkyl and R<sub>26</sub> is hydrogen or lower alkyl,

5 or R<sub>22</sub> and R<sub>24</sub> taken together are a fused benzene ring.

5. A compound according to claim 4, wherein R<sub>22</sub> is hydrogen (when R<sub>23</sub> is other than hydrogen), lower alkyl or halogen.

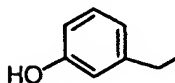
6. A compound according to claim 4 or claim 5, wherein R<sub>24</sub> is hydrogen, hydroxy, lower alkylsulfonyl, lower alkyl, halogen, nitro or lower alkoxy or a  
10 group of the formula:



wherein R<sub>25</sub> is unsubstituted or hydroxy-substituted phenyl lower alkyl, and R<sub>26</sub> is hydrogen,

or R<sub>22</sub> and R<sub>24</sub> taken together are a used phenyl ring.

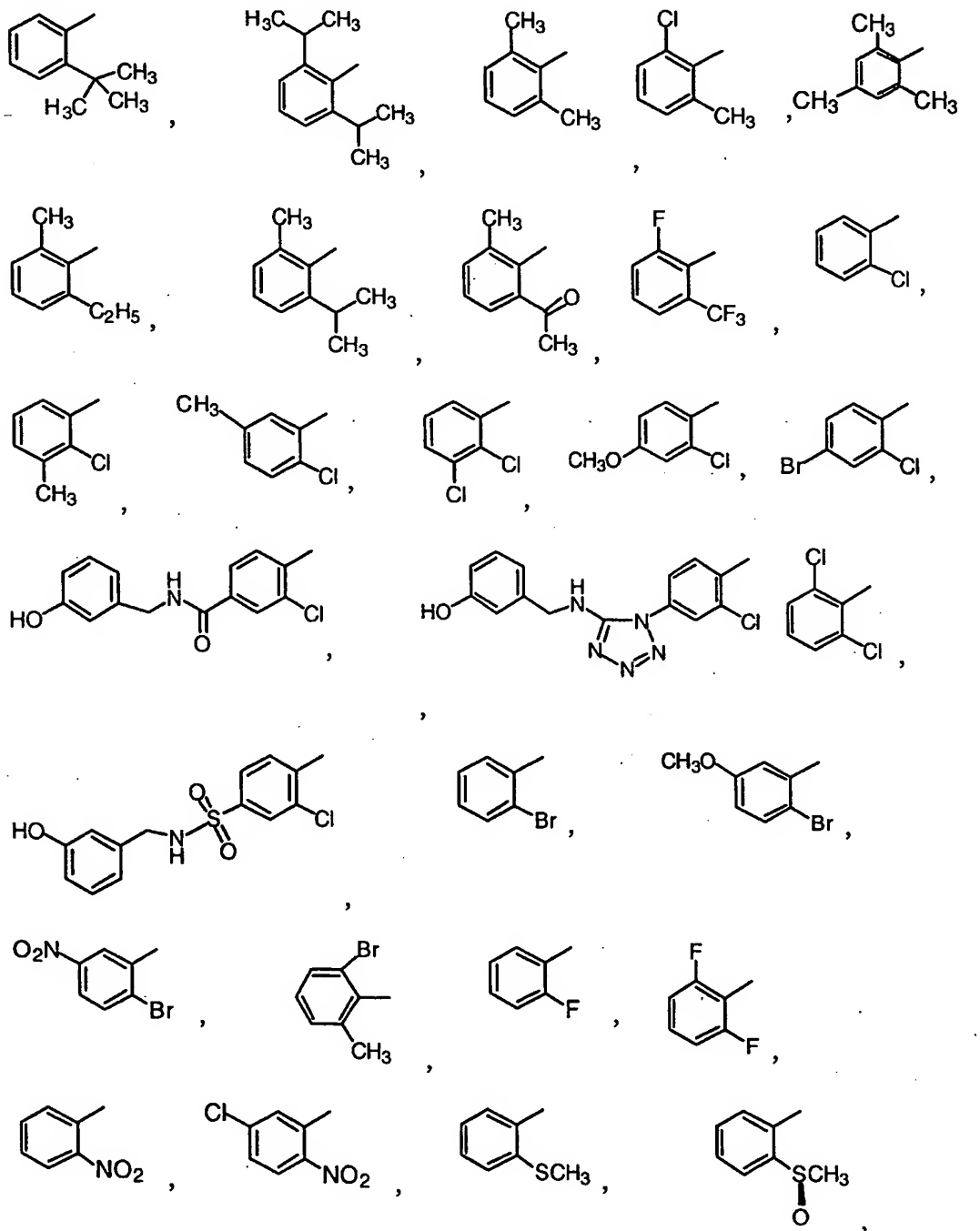
15 7. A compound according to claim 6, wherein R<sub>24</sub> is hydrogen, hydroxy, amino, methyl, chloro, bromo, nitro, -OCH<sub>3</sub>, -SO<sub>2</sub>CH<sub>3</sub> and R<sub>26</sub> is H and R<sub>25</sub> is



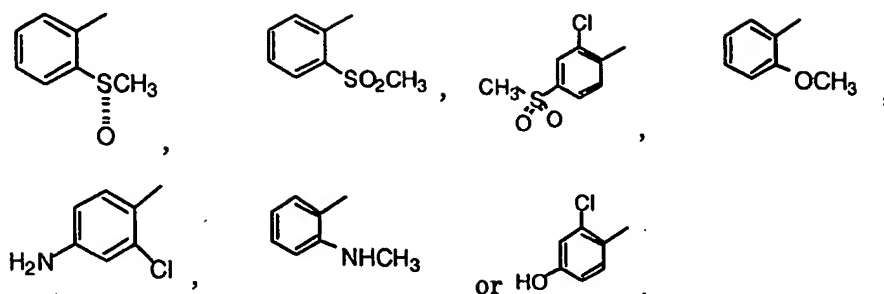
8. A compound according to any one of claims 4-7, wherein R<sub>23</sub> is hydrogen (when R<sub>22</sub> is other than hydrogen), lower alkyl, lower alkylamino,  
20 halogen, nitro, perfluoro lower alkyl, lower alkoxy, lower alkanoyl, lower alkylsulfinyl or lower alkyl sulfonyl.

9. A compound according to claim 8, wherein R<sub>23</sub> is methyl, ethyl, isopropyl, tertbutyl, trifluormethyl, chloro, bromo, fluoro, nitro, -COCH<sub>3</sub>, -SCH<sub>3</sub>, -SOCH<sub>3</sub>, -SO<sub>2</sub>CH<sub>3</sub>, -NHCH<sub>3</sub> or -OCH<sub>3</sub>.

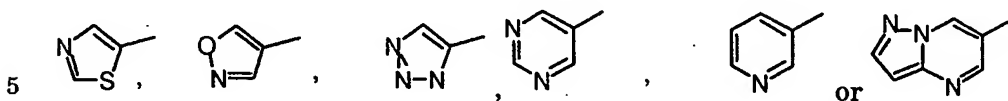
10. A compound according to any one of claims 4-9, wherein Y-1 is  
5 selected from the group consisting of:



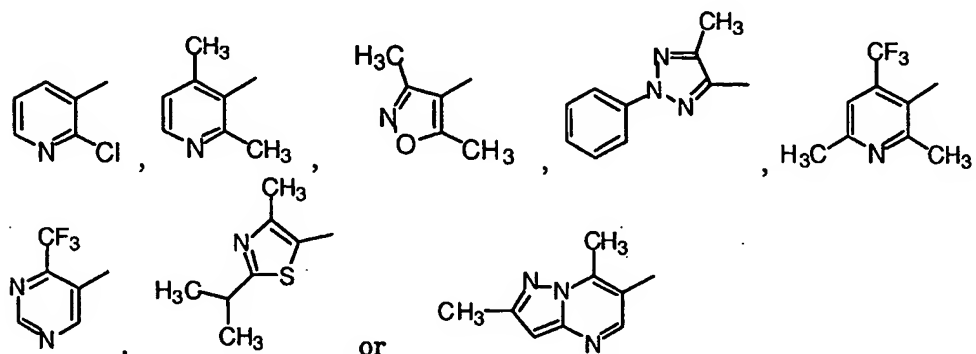
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11. A compound according to any one of claims 1-3, wherein in Y-2 the monocyclic heteroaromatic or the 9- or 10-membered bicyclic heteroaromatic groups are selected from the group of:



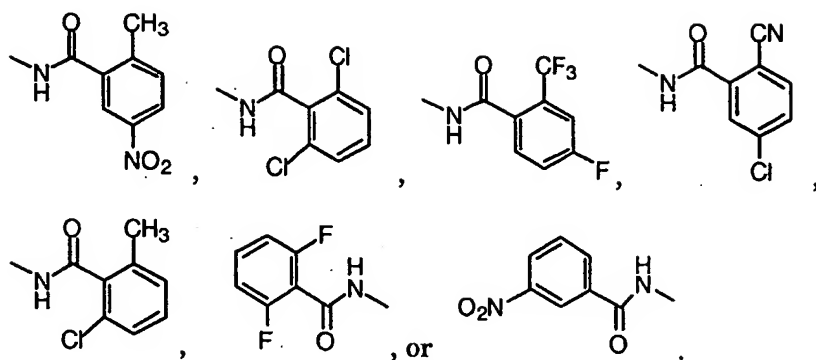
12. A compound according to claim 11, wherein groups Y-2 are of the formula:



13. A compound according to any one of claims 1-3, wherein in X-6 the groups R<sub>15</sub> and R<sub>16</sub> independently hydrogen lower alkyl, nitro, halogen, perfluoroloweralkyl, cyano or aryloxy.

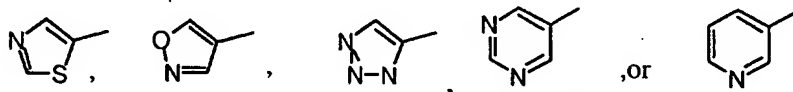
14. A compound according to claim 13, wherein R<sub>15</sub> or R<sub>16</sub> is H, methyl, nitro, chloro, fluoro, trifluormethyl, cyano or phenoxy.

15. A compound according to claim 13 or claim 14, wherein group X-6 is of the formula:



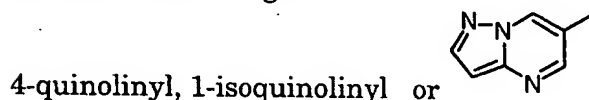
16. A compound according to any one of claims 1-3, wherein in X-7 Het is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3  
5 nitrogens, or a nitrogen and a sulfur, or a nitrogen and an oxygen.

17. A compound according to claim 16, wherein the heteroaromatic ring is



18. A compound according to any one of claims 1-3, wherein in X-7 Het is a bicyclic heteroaromatic ring containing from 1 to 3 nitrogens as the  
10 heteroatoms.

19. A compound according to claim 18, wherein the bicyclic heteroaromatic ring is



20. A compound according to any one of claims 1-3, wherein in X-7 R<sub>15</sub> is  
15 hydrogen, nitro, lower alkyl sulfonyl, cyano, lower alkyl, lower alkoxy, perfluorolower alkyl, lower alkylthio, lower alkanoyl, or aryl.

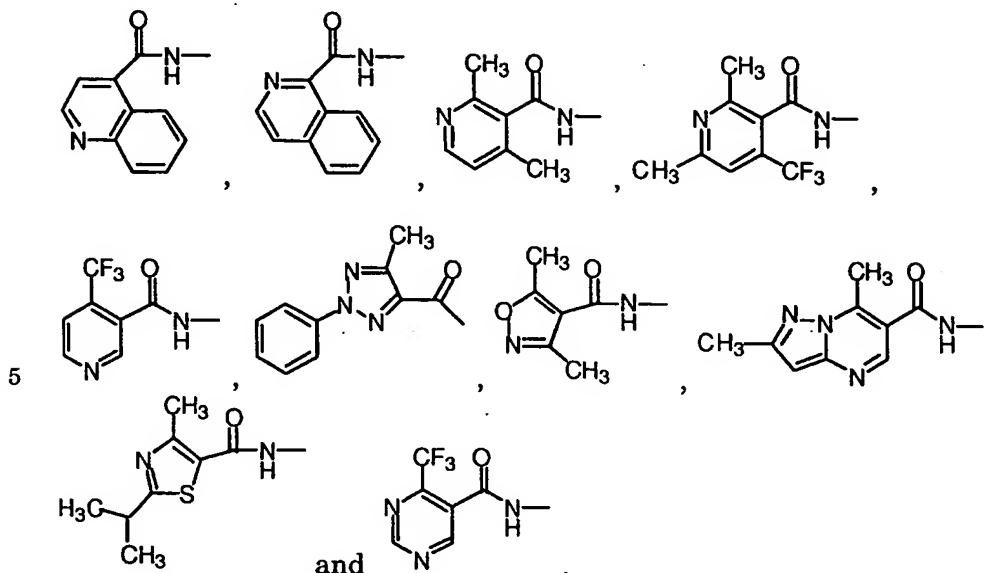
21. A compound according to claim 20, wherein R<sub>15</sub> is isopropyl, methyl or phenyl.

22. A compound according to any one of claims 1-3, wherein R<sub>16</sub> in X-7 is  
20 hydrogen, halogen, nitro, cyano, lower alkyl or perfluoro lower alkyl.

23. A compound according to claim 22, wherein R<sub>16</sub> is methyl or trifluoromethyl.

24. A compound according to any one of claims 1-3, wherein R<sub>30</sub> in X-7 is hydrogen or lower alkyl.





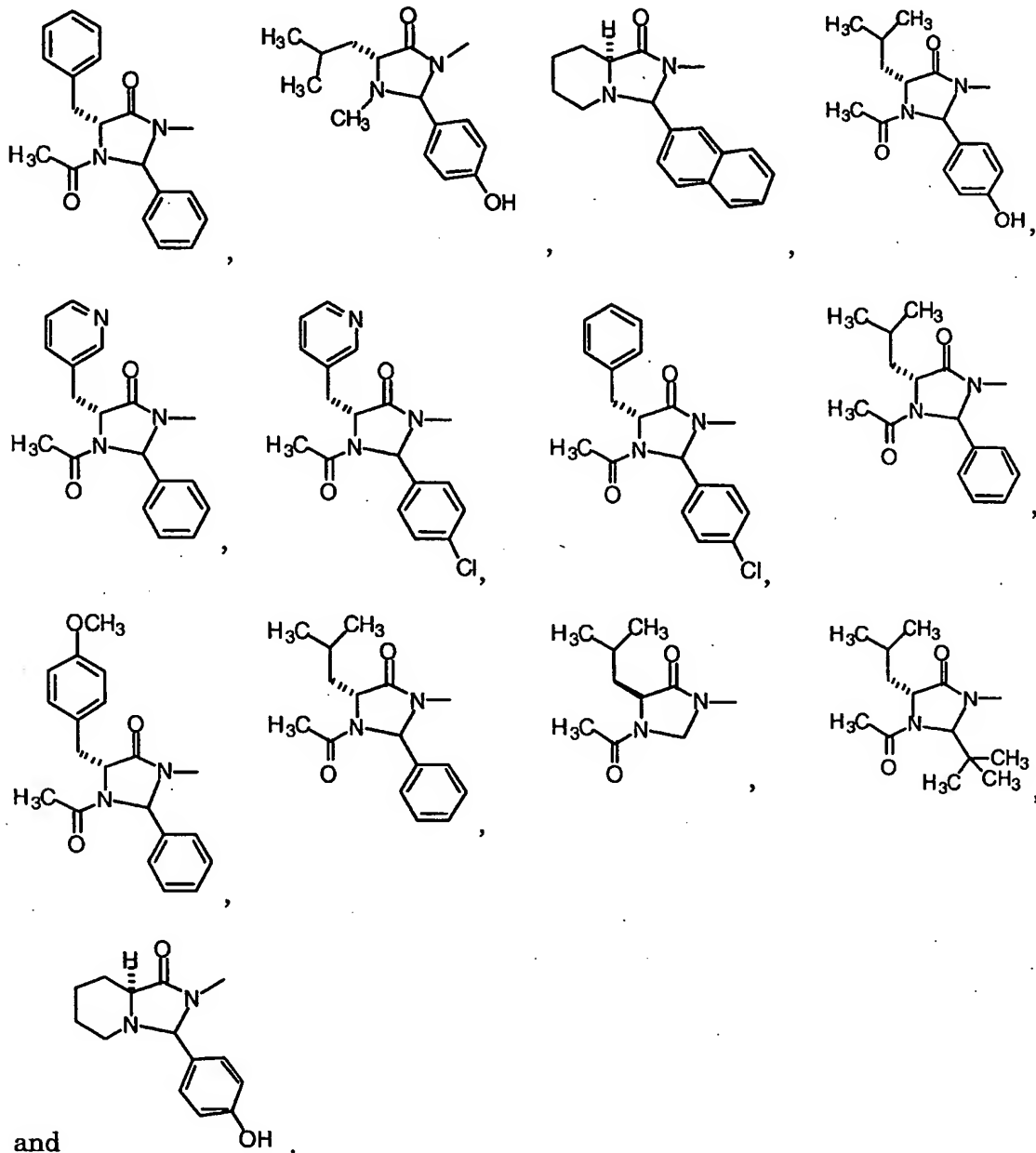
27. A compound according to any one of claims 1-3, wherein in X-6 or X-7  
10 a is 0.

29. A compound according to claim 28, wherein R<sub>18</sub> is tertbutyl, phenyl,  
15 phenoxy, chlorophenyl or phenylethyl.

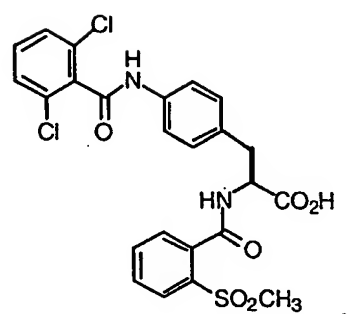
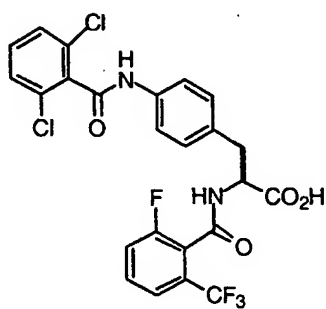
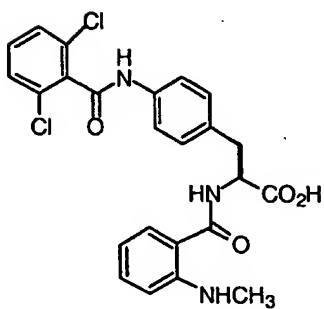
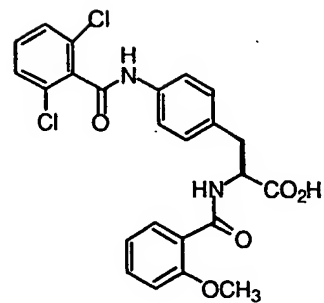
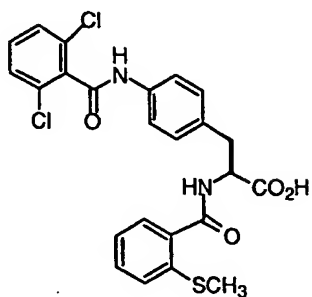
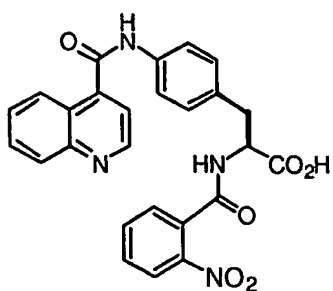
31. A compound according to claim 30, wherein R<sub>19</sub> is methyl, isobutyl, benzyl, 4-chlorobenzyl, 4-methoxybenzyl or 2-pyridylmethyl.

33. A compound according to claim 32, wherein R<sub>20</sub> is acetyl.

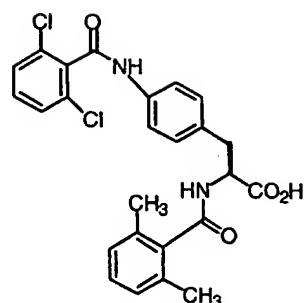
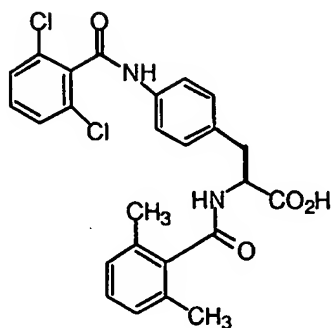
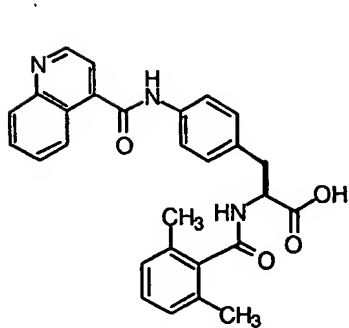
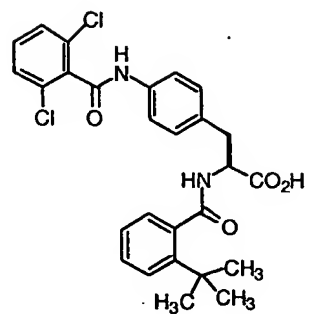
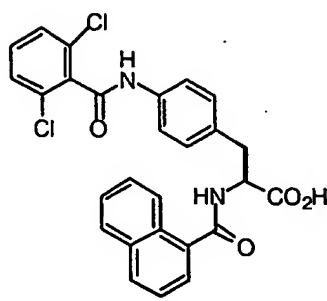
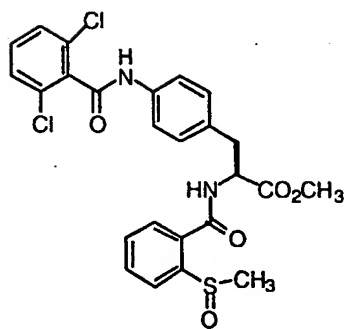
34. A compound according to any one of claims 1-3, wherein groups X-10 are of the formula:

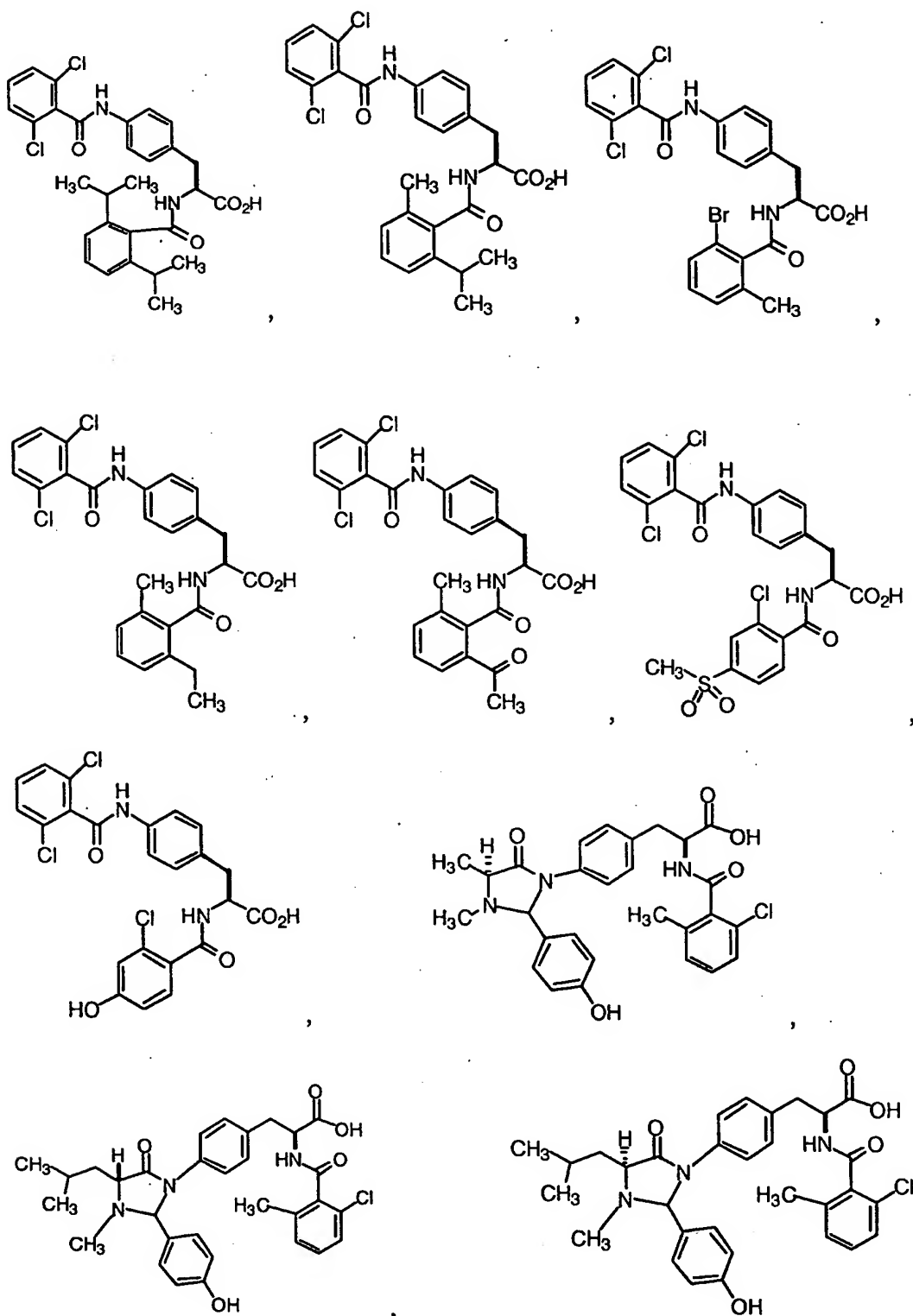


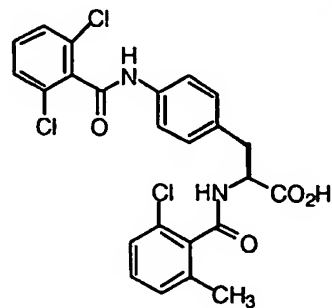
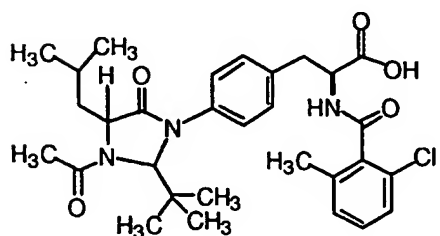
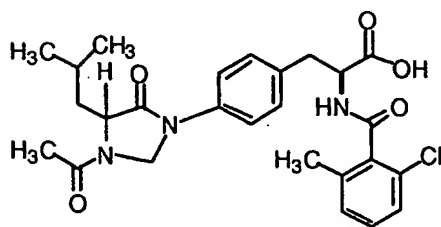
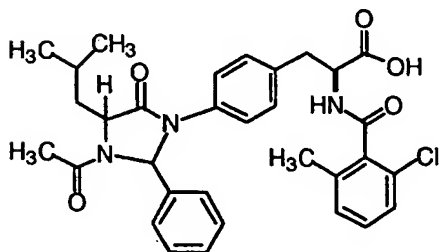
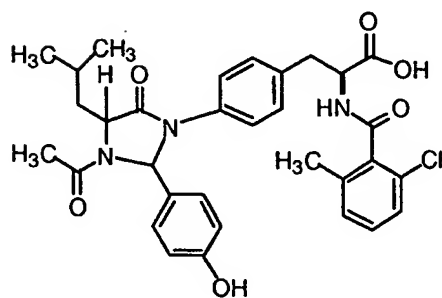
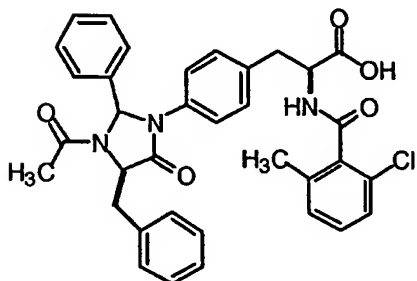
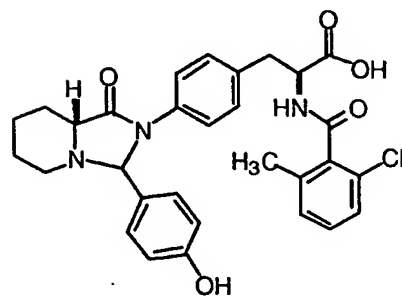
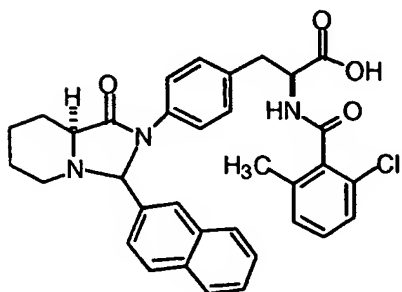
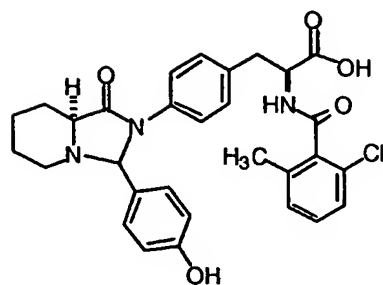
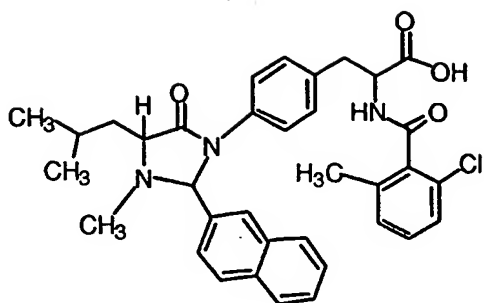
35. A compound selected from the group:

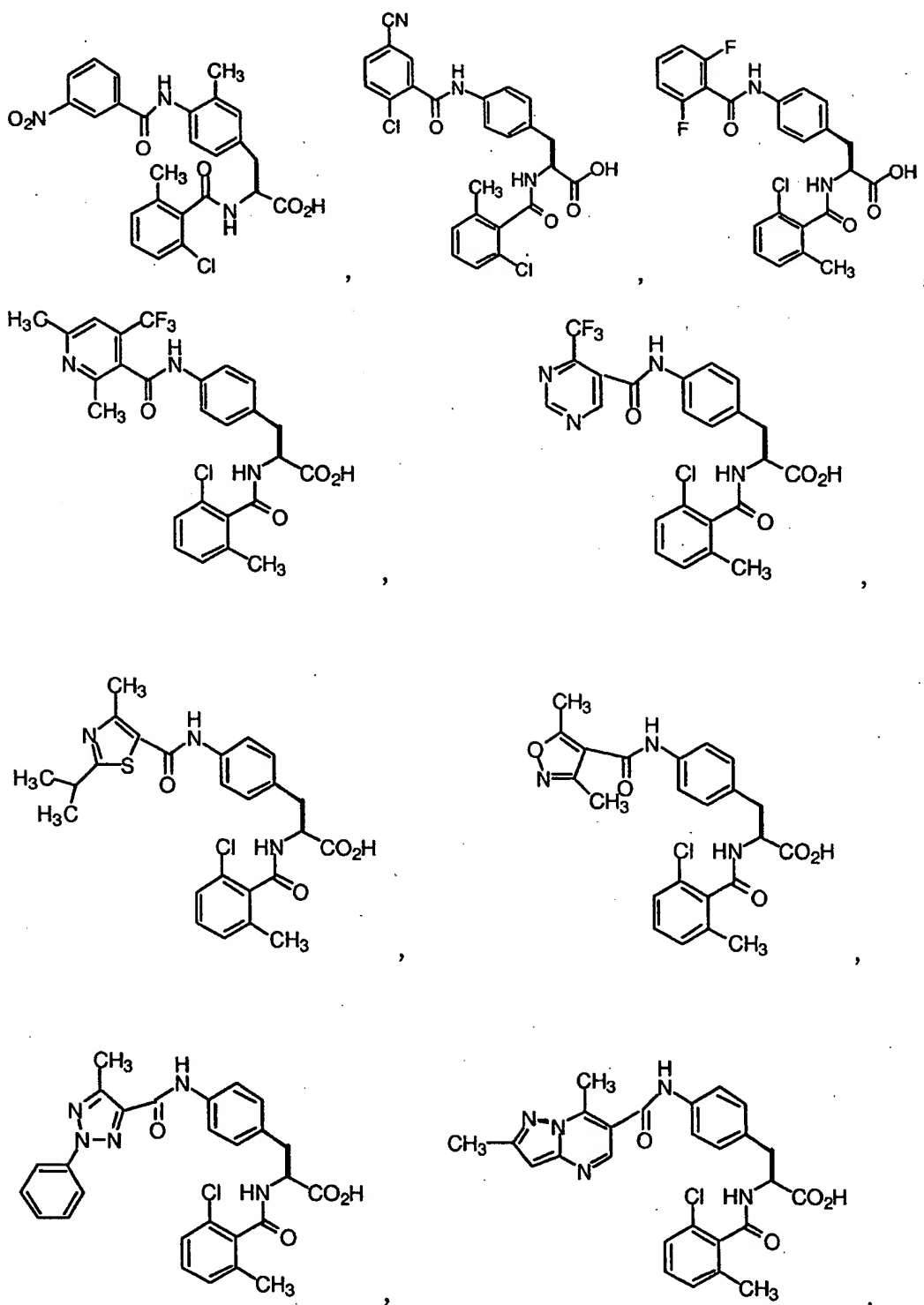


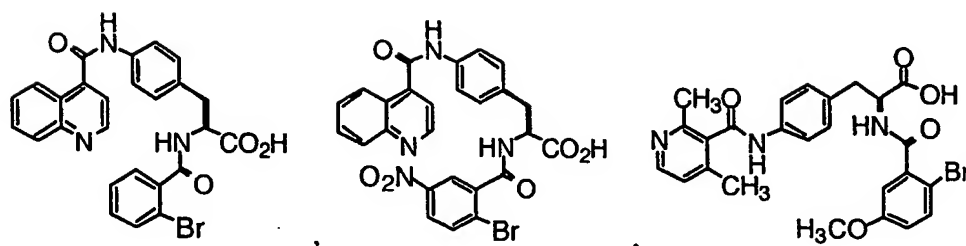
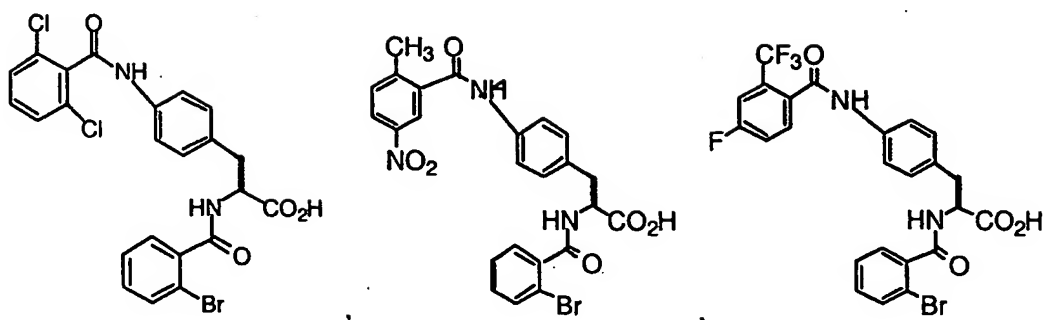
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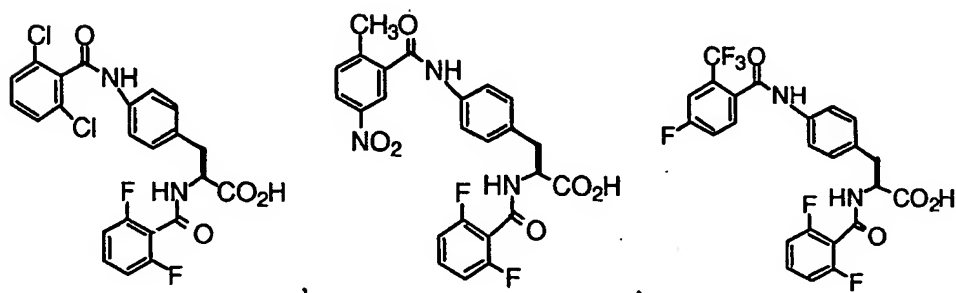
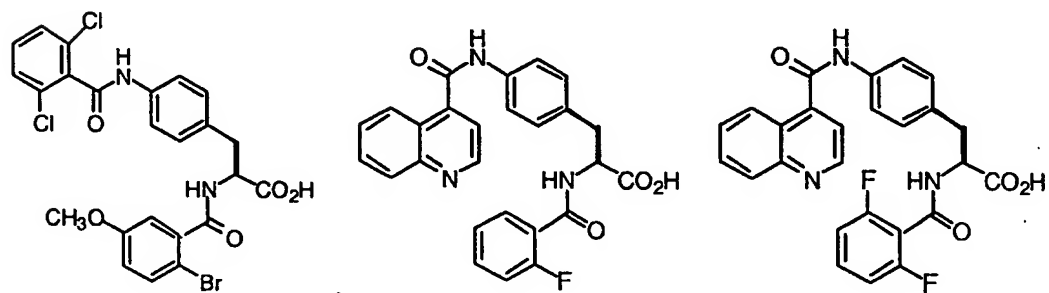


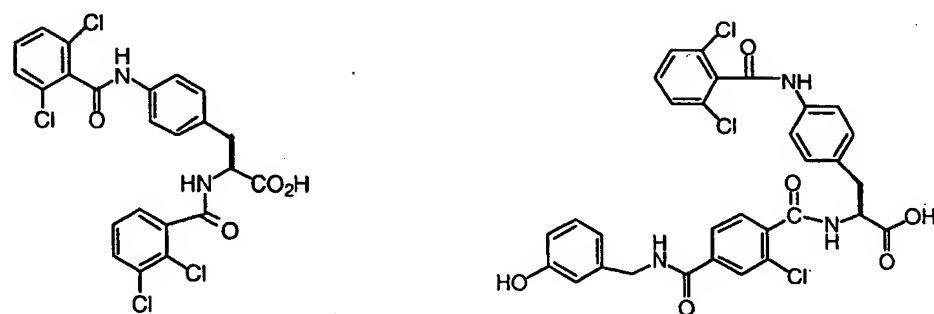
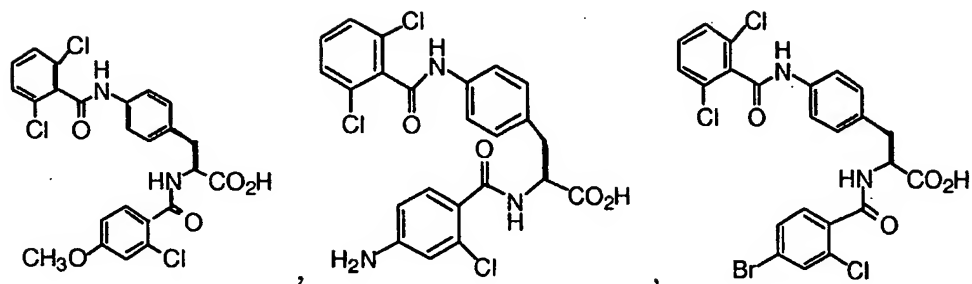
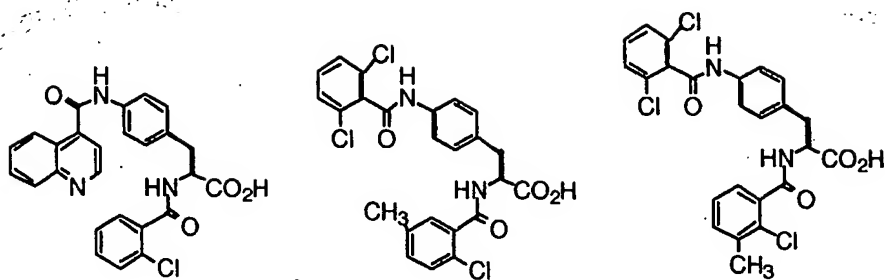




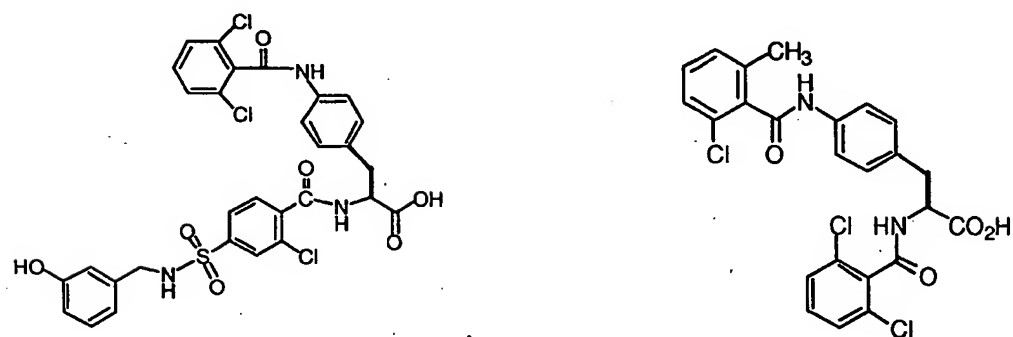


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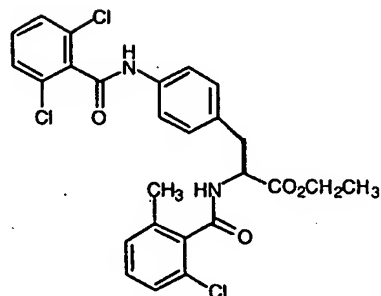
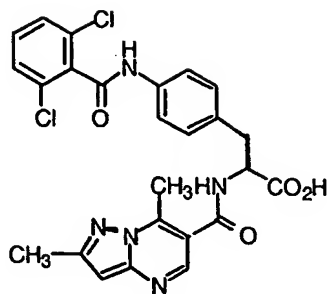
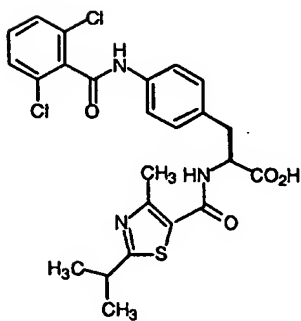
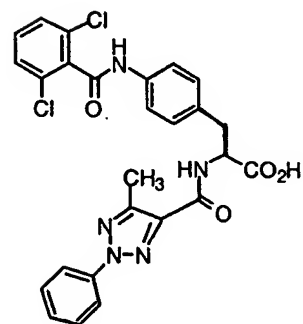
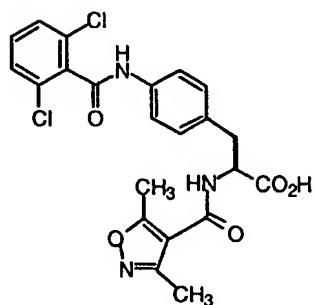
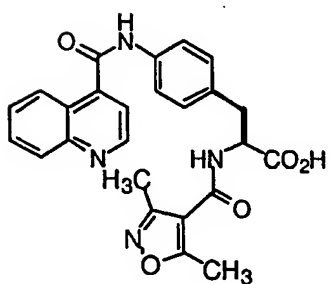
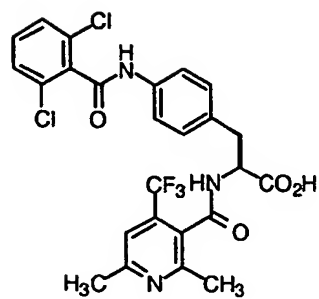
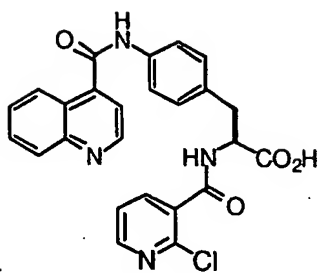
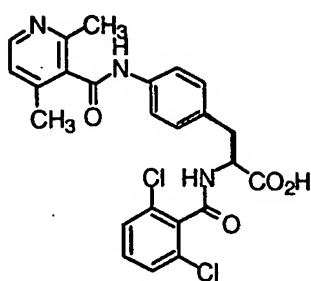




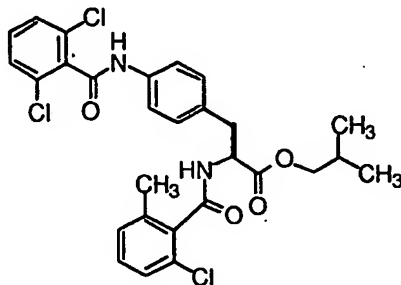
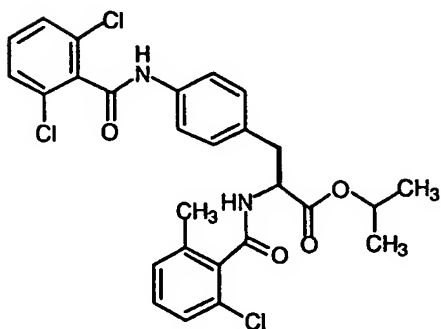
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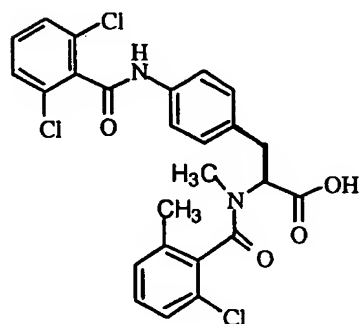
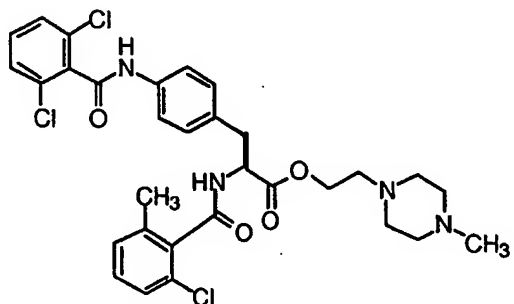
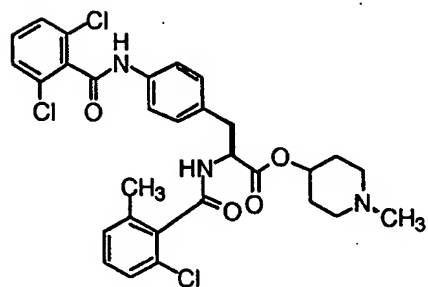
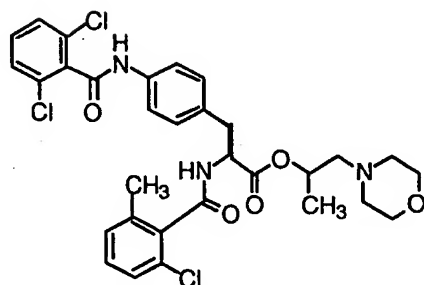
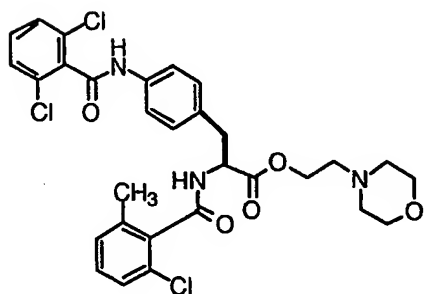
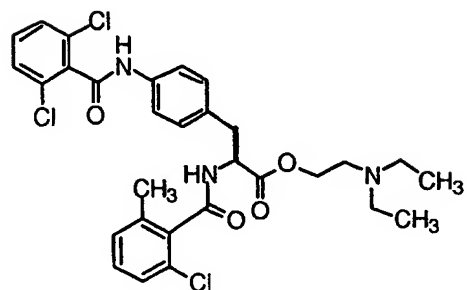
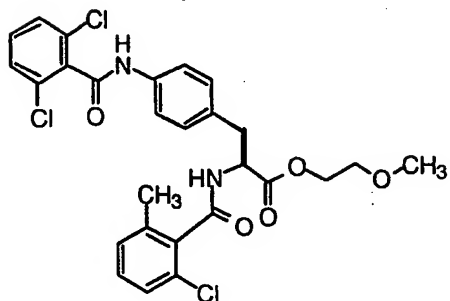
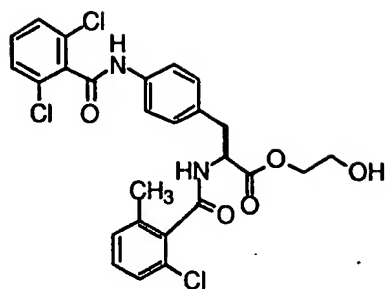
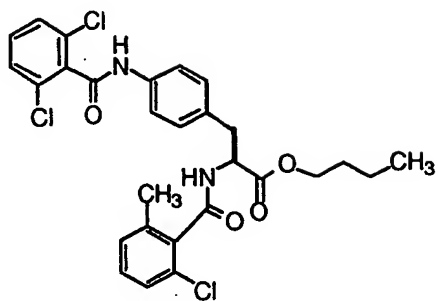






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36. Compounds according to any one of the claims 1-35 for use as a medicament.

37. Compounds according to any one of the claims 1-35 for use as a medicament in the treatment of rheumatoid arthritis, multiple sclerosis,  
5 inflammatory bowel disease or asthma.

38. A medicament containing a compound according to any one of claims 1-35 and a therapeutically inert carrier material.

39. A medicament for the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease or asthma, containing a compound  
10 according to any one of claims 1-35 and a therapeutically inert carrier material.

40. A process for the production of a medicament, especially for the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease or asthma, which process comprises bringing a compound according to  
15 any one of claims 1-35 into a galenical administration form together with a therapeutically inert carrier material and, if desired, one or more additional therapeutically active substances.

41. The use of a compound according to any one of claims 1-35 in the treatment of illnesses, especially in the treatment of rheumatoid arthritis,  
20 multiple sclerosis, inflammatory bowel disease or asthma.

42. Use of a compound according to any one of claims 1-35 in the preparation of a medicament for the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease or asthma.

43. The novel compounds, intermediates, processes, medicaments and  
25 methods as hereinbefore described.

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